Fecal Microbiota Treatment (FMT) Treatment for Patients who Experience Recurrent Episodes of *Clostridium difficile* infection (RCDI)
Introductory Statement

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Treatment Hypothesis

Patients who suffer recurrent episodes of RCDI have a high likelihood of resolving their relapsing diarrhea following fecal transplantation.

Background With Literature Review

Clostridium difficile infection (CDI) with colitis was first characterized in 1978.[1] Since then CDI has emerged as a common complication of antibiotic usage, and the leading cause of antibiotic-associated diarrhea, especially in institutional settings.[2-7] The severity of C. difficile infection ranges from mild cases, requiring little more than the discontinuation of antibiotics and supportive measures, to severe disease, with fever, elevated white blood cell count, toxicity and intractable diarrhea. Fatality rates as high has 24% have been reported in case series of critically ill patients with *C. difficile* colitis.[8, 9]

Recommended therapies for *C. difficile* infection include orally administered vancomycin or metronidazole. Treatment with either of these agents produce a clinical response in more than 90% of patients, and most patients have no further symptoms, even if the ongoing presence of *C. difficile* may be demonstrated in stool.

The principal problem encountered in the treatment of *C. difficile* colitis is recurrent diarrhea. The frequency of recurrence has been reported to be as low as 5% and as high as 50%; the overall risk of relapse is about 20%[2-4, 10]. Recurrent diarrhea may be caused by the persistence of *C. difficile* spores that have not been affected by treatment, or by reinfection with a new strain of *C. difficile.* It is difficult to predict which patients will experience recurrent infection, but there is increased risk for recurrence among older individuals, recent gastrointestinal surgery, prolonged hospital stay, especially in the intensive care unit, and individuals who have chronic comorbidities. However, once a patient has had a single relapse, the risk of subsequent relapses becomes significantly higher. As many as 26 relapses in a single patient have been reported.[2]

Recurrences of *C. difficile* colitis are generally treated with a repeat course of vancomycin or metronidazole. In many cases this therapy is successful. However, some patients develop a chronic, relapsing pattern of *Clostridium difficile* infection. In such patients, alternative therapies are needed. Treatment regimens that have been tried include vancomycin taper protocols, and newer agents such as rifaximin, nitazoxanide, and fidaxomycin. Unfortunately,

none of these approaches have been uniformly successful or emerged as a "standard therapy" for RCDI. Furthermore, the newer agents are expensive, and the wisdom of using antibiotics to treat a condition which was originally caused by the use of antibiotics must be questioned.

The medical literature contains a growing number of reports describing the success of reintroducing normal intestinal flora (FMT) into the intestinal tract of patients who have experienced recurrent *C. difficile* infection. Human stool collected from a healthy donor can be instilled *per rectum* in an enema preparation[25, 26], or into the proximal duodenum via a nasoduodenal catheter. FMT administered into the upper or lower GI tract have been highly effective in preventing recurrences of *C. difficile* infection, and 80-100% of patients treated with FMT are reported to be cured[28, 29]. The use of FMT has not been subjected to randomized controlled trials. The principal objection among medical providers to the use of FMT appears to be that the treatment "lacks aesthetic appeal"[27].

Preliminary Studies

A case series of 18 patients treated for recurrent *Clostridium difficile* infection at SMDC was published in 2003 (*Clinical Infectious Diseases 2003; 36:580-5).*[28] In this study, the medical records of 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection over a 9 year period at a single institution were reviewed retrospectively. During the time period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects had a total of 64 courses of antimicrobials (range 2-7, median 3). During the 90 days following the treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during the 90-day follow-up period. No adverse effects of the stool treatment were observed. The study concluded that patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors by nasogastric tube.

FMT Study Protocol

1. Patient Eligibility Criteria

(1) Age between 18 and 100 years
(2) Moderate CDI not responding to standard vancomycin therapy of at least one week duration
(3) Severe CDI not responding to standard therapy after 48 hours
(4) Laboratory confirmed diagnosis of recurrent *C. difficile* infection (two or more recurrences)
(5) Consent to receive FMT by NDT administration
(6) Sign an informed consent form and agree to return for a clinical evaluation and follow-up examination 3 – 4 weeks after FMT to document clinical improvement

Patient Exclusion Criteria: Causes of recurrent diarrhea not caused by *Clostridium difficile*. All patients who per eligibility criteria are candidates for FMT will be invited to participate in the stool specimen study.

2. Stool Donor Characteristics

All healthy individuals may be eligible for donating stool, unless they are disqualified by one or more specific exclusion criteria

Factors that reduce stool sample efficacy:

(1) The potential donor has received antibiotic therapy during the preceding 12 weeks
(2) History of major gastrointestinal surgery
(3) Use of systemic antineoplastic or immunosuppressive medication

Risk of transmission of occult infectious agent or comorbid condition:

(4) Known human immunodeficiency virus (HIV) infection
(5) Known viral hepatitis B or C infection
(6) High risk sexual behavior
(7) Use of illicit drugs
(8) Tattoos or piercing within the last 6 months
(9) History of inflammatory bowel disease (IBD) or GI malignancy
(10) History of systemic autoimmune disease

3. Donor Laboratory Screening: Potential donors must test negative for:

Stool testing

(1) *Clostridium difficile* (PCR or EIA test for Toxin A and B)
(2) Routine culture for enteric bacterial pathogens
(3) Complete Ova and Parasite studies, if pertinent travel history

Blood (serologic) testing

(4) anti-HIV type 1 and 2
(5) anti-HAV IgM
(6) HBsAg
(7) anti-HCV
(8) Rapid plasma reagin (RPR)

The medical records of all patients will be reviewed by Dr. Bakken. Data will be abstracted from the charts as described under "Data Management Plan" below. Data from the patients' charts will be entered into a database and analyzed as described under "Analysis Plan" below.

Setting

Candidate patients for FMT will be drawn principally from the patient population in northeastern Minnesota and northwestern Wisconsin. It is also anticipated that some patients will be referred from elsewhere in the U.S.A. Stool transplants will be conducted at St. Luke's Hospital in Duluth, MN. Data will be stored and analyzed at St. Luke's Hospital by Dr. Bakken.

Measurement Endpoints

The goal of FMT will be to resolve the recurrent episodes of diarrhea

Data Management Plan

Patients' medical charts will be examined by Dr. Bakken. For each of the patients, data on the following variables will be extracted from the medical records: age, gender, initial diagnosis (underlying illness for which antibiotics were used), type of antibiotic used (prior to the initial diagnosis of *C. difficile* infection), and date of initial episode of *C. difficile* infection. For each episode or recurrence of *C. difficile* colitis, the following data will be extracted: date of diagnosis of episode or recurrence, criteria used for diagnosis, treatment regimen used, date treatment regimen completed.

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